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Management of Sepsis in the First 24 Hours: Bundles of Care and Individualized Approach

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Abstract

Early diagnosis and prompt management are essential to enhance the outcomes of patients with sepsis and septic shock. Over the past two decades, evidence-based guidelines have guided appropriate treatment and recommended the implementation of a bundle strategy to deliver fundamental treatments within the initial hours of care. Shortly after its introduction, the implementation of a bundle strategy has led to a substantial decrease in mortality rates across various health care settings. The primary advantage of these bundles is their universality, making them applicable to all patients with sepsis. However, this same quality also represents their primary disadvantage as it fails to account for the significant heterogeneity within the septic patient population. Recently, the individualization of treatments included in the bundle has been suggested as a potential strategy for further improving the prognosis of patients with sepsis. New strategies for the early identification of microorganisms and their resistance patterns, advanced knowledge of antibiotic kinetics in critically ill patients, more conservative fluid therapy in specific patient populations, and early use of alternative vasopressors to catecholamines, as well as tailored source control based on patient conditions and site of infection, are potential approaches to personalize initial care for specific subgroups of patients. These innovative methodologies have the potential to improve the management of septic shock. However, their implementation in clinical practice should be guided by solid evidence. Therefore, it is imperative that future research evaluate the safety, efficacy, and cost-effectiveness of these strategies.

Keywords
- sepsis
- antibiotic
- bundles
- source control
- vasopressors
- fluid

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Bundles of Treatment and Source Control

For the past two decades, the management of patients with sepsis and septic shock has been informed by evidence-based recommendations from the Surviving Sepsis Campaign (SSC).[1,2] These recommendations have been implemented through bundles of care that emphasize key interventions to be completed within a specified time frame (►**Fig. 1**).[3] The original set of sepsis bundles proposed in 2004 consisted of resuscitation (five elements) and management (four elements) bundles to be completed within 6 and 24 hours, respectively. From the beginning, several of these recommendations have been questioned because of scarce evidence in support. Following a comprehensive evaluation of 32,000 patient records from 239 hospitals across 17 countries in 2013, the SSC proposed revisions of the original resuscitation bundles.[4] Specifically, the management bundle was discontinued, and the resuscitation bundle was restructured into a 3-hour bundle comprising four elements and a 6-hour bundle consisting of three elements. The data collected during this process indicated that the measurement of central venous pressure and oxygen saturation in the central venous blood was not critical for successful resuscitation. Consequently, these elements were removed from the resuscitation. In 2018, the SSC released an updated version of the bundle in accordance

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2005	2013	2018	Bundle Individualization
6-hour Resuscitation Bundle • Measure serum lactate • Obtain blood cultures prior to antibiotics within 3 hours of ED or 1 hour non-ED admission • With persisiting hypotension and/or serum lactate > 4 mmol/L Crystalloid 20 mL/kg Vasopressors if unresponsive • If persistent hypotension and/or serum lactate > 4 mmol/L CVP>8 ScvO2> 70% or SvO2>65% **24-hour Management Bundle** • Low dose steroids • Human activated protein C (rhAPC) • Blood glucose 70-150 mg/dl • Median inspiratory plateau pressure < 30 cmH2O	**3-hour Bundle** • Measure serum lactate • Obtain blood cultures prior to antibiotics • With hypotension and/or serum lactate > 4 mmol/L Crystalloid 30 mL/kg **6-hour Bundle** • Vasopressors for hypotension after fluid • For persistent hypotension after fluid or serum lactate > 4 mmol/L Measure CVP Measure ScvO2	**1-hour Bundle** • Measure serum lactate. Re-measure if initial > 2 mmol/L • Obtain blood cultures prior to antibiotics • Administer broad-spectrum antibiotics • Rapid crystalloid 30 mL/kg • Vasopressors if hypotension remains < 65 mm Hg after fluid resuscitation	**Antibiotic Therapy** • Fast microbiology for early targeted therapy in units with high prevalence of difficult to treat microorgansims. • Therapeutic drug monitoring in specific populations **Fluid resuscitation** • Restrictive fluid strategy in elderly surgical and ARDS patients **Vasopressors** • Early use of multimodal approach and alternatives to cathcolamines in patients requiring high dose of vasopressors **Source control** • Multidisciplinary approach • Time: early but not too early • Method: effective but not excessive

Fig. 1 Historical evolution of sepsis bundles of care and proposals for potential individualization in particular conditions and populations. ARDS, acute respiratory distress syndrome. CVP, central venous pressure; ED, emergency department; ScvO2, O2 saturation in central venous blood.

with the recommendations of the 2016 guidelines (edition).[3] The most significant change was the consolidation of the previous 3- and 6-hour bundles into a single "hour-1 bundle" with the intention of commencing resuscitation and management without delay. The five elements included were the assessment of lactate levels, blood cultures prior to antibiotic administration, broad-spectrum antibiotic therapy, administration of 30 mL/kg crystalloids to restore the target mean arterial pressure (MAP), and initiation of vasopressors if the target MAP was not achieved after fluid resuscitation. Several reports have shown that compliance with bundles is associated with reduced mortality risk in patients with severe sepsis and septic shock.[5,6] Despite some inconsistencies, a meta-analysis including 50 observational studies on the effect of performance improvement programs showed that they were associated with better adherence to sepsis bundles, along with a reduction in mortality (odds ratio [OR]: 0.66; 95% confidence interval [CI]: 0.61–0.72) in patients with sepsis and septic shock.[7] The connection between the bundles and survival was further established by a large observational study, which demonstrated a lower risk-adjusted in-hospital mortality rate when a 3-hour bundle of sepsis care was completed more quickly.[8] In their research, Seymour et al[8] examined the individual elements of the sepsis bundle and found that the time to antibiotic administration demonstrated temporal advantages comparable to those of finishing the whole bundle, whereas fluid resuscitation did not display such benefits. Based on the outcomes outlined above, evidence-based guidelines strongly recommend that standard operating procedures, which are derived from early goal-directed therapy and incorporate elements of the sepsis bundle, should be incorporated into clinical practice as an effective means of enhancing patient outcomes and appropriate treatment.[2]

Although not included in the sepsis bundle, it is crucial to consider source control as a fundamental pillar of management, alongside antibiotic therapy and resuscitation for patients with sepsis. Sepsis diagnosis entails the recognition of organ dysfunction and identification of the causative infection, including its site and microorganism.[9] In the process of source identification, the patient's medical history, including comorbidities, immunosuppression, recent surgery, and other relevant factors, is considered, along with clinical evaluation and targeted imaging techniques, such as conventional imaging, ultrasound, and CT scans. Respiratory tract infections are the most common cause of sepsis, followed by abdominal and urinary tract infections, as reported in the literature.[10] Current guidelines emphasize the need for prompt identification of the specific anatomical site of infection that requires source control and implementation of the required source control intervention as soon as medically and logistically feasible.[2] Moreover, the removal of intravascular access devices that may serve as a potential source of sepsis or septic shock is recommended. The optimal duration for source control has not yet been established, despite evidence suggesting that a period of 6 to 12 hours may be beneficial.[11–16] The factors that prevented the integration of source control measures into the sepsis bundle were unclear optimal approach and timeline for implementation at specific infection sites.

Individualized Therapy in the First 24 Hours

Heterogeneity in sepsis is a persistent challenge for effective identification and treatment of patients. Several factors contribute to this heterogeneity, including the type of infectious agent, site of infection, host response, and the treatment interventions used.[17] Ideally, therapeutic interventions should

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positively affect the pathobiological cascade and ultimately influence the patient's clinical course. However, different treatments may have varying effects on specific patient subpopulations, further complicating sepsis management. Sepsis bundles were devised for the express purpose of simplifying the early detection and treatment of sepsis in patients.[3] These bundles are intended to be universally applicable to all patients with sepsis, which is their main advantage. However, this also represents a principal drawback as the bundles do not consider the considerable heterogeneity of the septic population. Recently, there has been a growing demand for a more individualized approach to treating patients with sepsis within the scientific community.[18,19] The following sections focus on evaluating recent advancements in specific aspects of personalized care for patients with sepsis.

Individualized Antibiotic Therapy

Antibiotic therapy in combination with source control remains a key component of sepsis management. Appropriate antibiotic therapy in terms of timing, molecules, and dosage has been demonstrated to significantly reduce the risk of mortality in septic shock.[20] To provide adequate coverage against infectious microorganisms, broad-spectrum antibiotics are frequently administered from the diagnosis of sepsis/septic shock until the identification and definition of the antibiotic susceptibility pattern, which typically takes 36 to 96 hours using standard microbiological methods. This approach can expose patients to large cumulative doses of broad-spectrum antibiotics, increasing the risk of developing antibiotic resistance.[21] This phenomenon is exacerbated and amplified in areas with a high prevalence of multidrug-resistant organisms, leading to the spread of bacterial infections that are caused by difficult-to-treat bacteria.[22] A similar approach can be applied to fungal infections and antifungal therapy, with increasing resistance to commonly used antifungal therapy and the emergence of highly resistant yeasts, such as *Candida auris*.[23]

In recent years, new technologies have been developed for the early identification of infectious agents and their possible resistance mechanisms, particularly in respiratory tract infections.[24,25] This may allow the provision, within hours, of quasi-targeted therapy or withdrawal of antibiotic therapy in cases such as viral pneumonia. These new methods are fundamental for the timely personalization of antibiotic therapy and for decreasing the burden of antibiotic overuse and the related emergence of difficult-to-treat bacteria.[22] Nevertheless, to achieve clinically significant outcomes, the application of these techniques in clinical settings mandates the interpretation of findings by experts, and it is crucial to incorporate them into established antimicrobial stewardship programs.[26]

Over the past few years, it has become increasingly clear that choosing the appropriate antibiotic dosage is also an essential factor for achieving a clinical cure and reducing the emergence of resistant strains.[27] Various factors, such as pharmacological characteristics, patient clinical conditions, and methods of administration, can affect the concentration of antibiotics at the site of action, which in turn affects the efficacy of the antibiotic in combating microorganisms.[28] To ensure optimal treatment, it is crucial to carefully evaluate all variables to determine the most suitable antibiotic dose. Furthermore, in patients with specific clinical conditions such as high renal clearance, microorganisms with a high resistance profile, and drugs with varying metabolism, it may be necessary to assess drug blood concentrations to establish the correct dosage. These considerations emphasize the significance of individualized treatment in septic patients.[29]

Individualized Fluid Resuscitation

As previously mentioned, the 2021 edition of the guidelines recommends administering at least 30 mL/kg of intravenous crystalloid fluid within the first 3 hours of resuscitation. It is also recommended to use dynamic variables, including passive leg raise, fluid bolus, stroke volume variation, echocardiography, and serum lactate levels, to assess fluid responsiveness and prevent fluid overload during resuscitation. It has been proven that a higher volume of fluid in the initial hours, but a lower volume over the course of 24 hours, decreases mortality in patients with severe sepsis and septic shock, and that a positive total fluid balance increases mortality by a factor of 1.7.[30] Additionally, a positive fluid balance between 5 and 10 L in the first 48 hours after damage-control laparotomy is an independent risk factor for developing enteric fistula and abdominal sepsis in patients with an open abdomen.[31] As a result, fluid therapy approaches have shifted from massive fluid resuscitation to more restrictive strategies.[32,33] For many years, permissive hypotension with small-volume resuscitation has been recommended to manage hemorrhagic shock and reduce fluid overload and its associated complications. A recent randomized controlled trial evaluated a permissive hypotension strategy (MAP: 60–65 mm Hg) against standard care (MAP: 75–80 mm Hg) in 118 patients with septic shock. The results demonstrated that among older patients, there was a decrease in in-hospital mortality in the permissive hypotension group.[34] A randomized controlled trial conducted in 2,463 patients aged >65 years with septic shock revealed that adopting a permissive hypotension strategy (MAP: 60–65 mm Hg) resulted in reduced utilization of vasopressors compared with conventional care, without any significant variation in 90-day mortality rates (41.0 vs. 43.8%).[35] The Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care[36] and the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis[37] trials were designed to address whether restrictive versus liberal fluid administration would improve outcomes in patients with sepsis and septic shock. In the restrictive arm, additional fluid administration was allowed if signs of severe hypoperfusion were present: lactate level >4 mmol/L, MAP <50 mm Hg, extensive mottling, or urine output <0.1 mL/kg/h. In both trials, no disparity was observed in the primary outcome measure of the 90-day mortality. Additionally, a meta-analysis of studies examining the effects of a restrictive versus liberal fluid strategy after initial resuscitation in sepsis revealed that the restrictive approach was associated with a reduction in the duration of mechanical ventilation without any discernible impact on mortality.[38]

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The above outcomes indicate that a fluid-restrictive approach is secure and may be particularly beneficial for individuals who are at risk for complications arising from fluid overload, such as surgical patients and those with acute respiratory distress syndrome.

Individualized Vasopressor Therapy

Septic shock causes significant disruption of both the macro- and microcirculation, resulting in a decline in tissue perfusion and oxygenation. Fluid resuscitation with crystalloids and norepinephrine is commonly performed in most patients. In cases of profound vasoplegia,[39] high doses of noradrenaline may be necessary to maintain perfusion pressure, which may increase the risk of catecholamine-related adverse events, such as tachycardia, cardiac dysfunction, and peripheral vasoconstriction.[40,41] Additionally, high doses of vasoactive amines can significantly alter regional perfusion, cell metabolism, and immune responses.[42–45] To reduce or prevent the adverse effects of excessive dosages of vasoactive amines, a catecholamine-sparing strategy that includes the use of steroids and alternative vasopressor drugs has recently been suggested.[46,47] Different nonadrenergic vasopressors have recently been proposed for septic patients, and many reports suggest that a multidimensional approach may be more suitable than the monodimensional approach proposed in bundles and guidelines.[48–50] Based on its pharmacological properties and available evidence, vasopressin is recommended as a secondary vasopressor in patients who are unresponsive to noradrenaline.[2] Although its use has not been linked to improved mortality rates, it appears to decrease the likelihood of arrhythmias and the need for renal replacement therapy. Additionally, there was no increase in adverse events, except for digital ischemia.[51] In the treatment of refractory septic shock, Angiotensin II has been shown to effectively restore MAP in approximately two-thirds of patients,[52] without evident impacts on mortality rates or adverse events. Additionally, secondary analyses have suggested that the use of Angiotensin II as a second or third vasopressor may decrease the risk of mortality in specific subgroups of patients, such as those with acute renal failure, elevated renin levels, and low vasopressor doses.[48] In summary, adopting a personalized vasopressor strategy that incorporates a multimodal approach and employs alternatives to noradrenaline appears to be advantageous for specific patient groups with septic shock. However, additional evidence is required to validate this approach.

Individualized Source Control

When identifying a source, commonly posed questions among intensive care unit (ICU) physicians typically pertain to "how" and "when" to manage or control the identified source. Ideally, the best method should be effective and rapid, without the need for surgery (and therefore anesthesia), without the need for transportation, and not cause worsening of physiological derangement. Regrettably, the extensive diversity of variables, such as the location and intensity of the infection and the individual's clinical status, creates uncertainty regarding the optimal method for managing the source of infection in each septic patient. Furthermore, other factors need to be considered, such as accessibility and expertise of the surgeon and interventional radiologist.[9] Consequently, adopting a tailored and multidisciplinary approach that allows patient-specific decisions to consider all the relevant factors is recommended.

When evaluating the optimal timing for intervention, the available evidence primarily comprises retrospective studies, which are often plagued by methodological limitations, and have primarily been conducted in cohorts of patients with intra-abdominal infections or necrotizing fasciitis,[11–13,53] thus making it difficult to generalize these findings. A prospective, observational, multicenter cohort study in 44 German ICUs evaluated the impact of time to antibiotic therapy, time to source control, and adequacy of antibiotic therapy in 1,011 patients with severe sepsis or septic shock.[14] The authors found that a delay in surgical or interventional source control of >6 hours was associated with increased mortality (42.9 vs. 26.7%, $p < 0.001$). A large prospective observational analysis evaluated the impact of timing on source control in 3,663 patients with severe sepsis or septic shock in 99 surgical-medical ICUs in Spain.[15] The authors demonstrated that patients who underwent source control measures had lower mortality rates in the adjusted analysis (OR: 0.81; 95% CI: 0.66–0.99, $p = 0.044$), despite higher disease severity at baseline. In this study, the median time to source control was 4.6 hours (interquartile range [IQR]: 1–11.5 hours). Notably, the authors did not establish a connection between the source control measures performed after 12 hours and increased mortality. One possible reason for this observation could be that the clinical team considered source control measures to be more pressing in patients who had earlier source control measures, and this factor was not considered in the multivariate analysis. In patients with sepsis, source control may be postponed because small infection sites might not be apparent during the initial evaluation or physicians might have delayed source control in patients who were more stable. A post hoc analysis conducted in a multinational observational study (Abdominal Sepsis Study), which involved 2,621 adult patients with intra-abdominal infections from 306 ICUs across 42 countries, revealed that urgent source control, performed within 2 to 6 hours, was associated with increased odds of survival, while emergency source control, performed within 2 hours or delayed later than 6 hours, was not.[16] The appropriateness of empirical antimicrobial treatment did not significantly affect survival, suggesting that source control may be more determinative of the outcome. In conclusion, evidence indicates that prompt source control improves survival; however, careful evaluation of the appropriate timing is necessary for each individual case. In certain situations, a temporary strategy may be more appropriate. The timing may be determined by physiological factors, and some patients may be unwell enough to undergo major surgery within the first hour. In such cases, less invasive strategies may be performed as an initial step. Although this approach can often provide temporary control of the infection source, definitive intervention should not be delayed when the patient has improved, because inadequate source control can lead to persistent infection, sepsis, and septic shock. In

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such cases, a more aggressive approach may be necessary, and should not be postponed.

Upon completion of source control, the most commonly posed question is whether the source control has been successfully executed. Several methods can be employed to evaluate the suitability of source control, including clinical evaluation, biomarker measurement, and targeted radiological imaging. Patients with inadequate eradication of infectious sources often show no improvement or worsening of clinical conditions after the initial management, with the persistence of systemic inflammation and organ failure. Commonly used biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) may help identify the conditions in question. However, injury caused by surgery, which disrupts physiological barriers, can initiate a systemic inflammatory response, making it difficult to attribute the clinical and biochemical signs of infection specifically to the persistence of the infection. This limitation in specificity was observed during the postoperative phase. PCT has been widely studied and found to be more sensitive than other biomarkers when used as an early indicator of uncontrolled infection after major surgery.[54–57] Additionally, its dynamic changes, rather than the concentration, may be more important in this regard.[58] In summary, the management of source control in sepsis requires a personalized approach and collaboration among team members. A multidisciplinary approach that includes the participation of surgeons, infectious disease physicians, interventional radiologists, interventional endoscopists, anesthesiologists, and intensivists is crucial for determining the most effective source control strategy for each individual patient. Timing is crucial for source control, and prompt intervention should be performed while considering the patient's physiological status. It is also essential to continuously reassess patients to identify potential inadequacies and failures in controlling the infection.

Conclusion

The use of a protocolized methodology that incorporates treatment bundles to manage the initial hours of patients with sepsis and septic shock has been demonstrated to enhance survival rates. However, the mortality rate associated with septic shock remains significant, particularly in specific subgroups such as those with severe preexisting comorbidities or multiple organ failure. To achieve further improvements in patient outcomes, individualization of the treatment components included in the bundle and source control measures have been suggested. In recent years, new technologies for early microorganism identification and definition of antibiotic resistance patterns, less aggressive fluid resuscitation, and the early use of a multimodal approach with an alternative to noradrenaline in specific patient categories seem to be promising strategies for individualizing the care of septic shock patients in the first hours. Similarly, an individualized approach to source control, defined by a multidisciplinary team with a less aggressive timeframe and methods for severely ill patients, is advisable. Although these innovative approaches show promise in enhancing the management of septic shock, their routine use in clinical practice must be confirmed by robust evidence. It is crucial that future studies assess the safety, efficacy, and cost-effectiveness of these strategies in diverse patient populations to determine whether they offer a clear benefit over current standards of care.

Conflict of Interest

M.G. has received honoraria for speaking at conferences and advisory services from Biomerieux, Thermofischer, Pfizer, MSD, Gilead, Shionogi, AOP Pharma, and Viatris related to the topic of this study. The other authors declare that they have no conflict of interest related to the topic of this study.

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